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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,527	10/19/2001	Raymond A. Dwek	2543-1-023	1260

7590 11/05/2002

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/05/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/042,527	Applicant(s) DWEK ET AL.	
	Examiner Daniel M Sullivan	Art Unit 1636	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9-11,14,15,25-28,33-35 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-11,14,15,25-28,33-35 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is a First Office Action on the Merits of the Application filed October 19, 2001, which is a Continuation of PCT/GB00/01560, filed April 20, 2000, and claims priority to United Kingdom Application 9909066.4, filed April 20, 1999. This action is a response to the Election filed August 19, 2002 (Paper No. 6) in response to the Restriction Requirement mailed July 16, 2002 (Paper No. 4). Claims 5-8, 12, 13, 16-24, 27-32, 36 and 37 were canceled in Paper No. 6. Claims 1-4, 9-11, 14, 15, 25-26, 33-35 and 38 are pending and under consideration in the Application.

Election/Restrictions

Applicant's election of Group I (Claims 1-4, 9-11, 14, 15, 25-28, 33-35 and 38) and the species Gaucher disease in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United Kingdom on April 20, 1999. It is noted, however, that applicant has not filed a certified copy of the 9909066.4 application as required by 35 U.S.C. 119(b).

Drawings

The drawings are objected to for the reasons indicated on the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9-11, 14, 15, 25, 34, 25 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claims encompass a method for treating a glycolipid storage-related disorder comprising administering "an inhibitor of glycolipid synthesis" and compositions to be used in the claimed method which comprise said inhibitor of glycolipid synthesis. Therefore, the inhibitor of glycolipid synthesis is a critical element of both the method and composition. The Revised Interim Guidelines state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately

described in the specification and which is not conventional in the art" (Column 3, page 71434). Given its broadest reasonable interpretation, the limitation inhibitor of glycolipid synthesis encompasses a broad genus of any and all compounds capable of inhibiting glycolipid synthesis in a cell. This genus would include inhibitors of enzymes involved in synthesis of more complex glycolipids, as well as crebroside, and inhibitors of enzymes that make the lipid and sugar substrates of the enzymes directly involved in glycolipid synthesis. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). The specification provides a detailed description reduction to practice of imido sugar compounds capable of inhibiting glucosylceramide synthase (see especially paragraph 51 and the Examples). The specification does not describe inhibitors of enzymes involved in synthesis of glycolipids other than glucosylceramide synthase. The specification fails to teach the chemical or physical structures of inhibitors of enzymes other than glucosylceramide synthase or the common attribution of the genus of any and all compounds capable of inhibiting glycolipid synthesis.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* inhibitors of glycolipid synthesis. Therefore, only the described glucosylceramide synthase inhibitors meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-4, 9-11, 14, 15, 25, 26, 33-35 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating type I Gaucher disease comprising administering a therapeutically effective amount of an inhibitor of glycolipid synthesis in combination with an agent capable of increasing the rate of glycolipid degradation, wherein the inhibitor of glycolipid synthesis is an inhibitor of glucosylceramide synthase and the agent capable of increasing the rate of glycolipid degradation is a glucocerebrosidase enzyme, and a composition comprising an inhibitor of glucosylceramide synthase with a glucocerebrosidase enzyme, does not reasonably provide enablement for a method of treatment of any and all glycolipid storage-related disorders comprising administering any and all inhibitors of glycolipid synthesis in combination with any and all agents capable of increasing the rate of glycolipid degradation, or compositions comprising any and all inhibitors of glycolipid synthesis in combination with any and all agents capable of increasing the rate of glycolipid degradation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or

use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The invention contemplates treating glycolipid storage-related disorders using combination therapy, wherein an inhibitor of glycolipid synthesis and an agent capable of increasing glycolipid degradation are co-administered.

Breadth of the claims: The claims encompass a method of treating any and all glycolipid storage-related disorders comprising administering a therapeutically effective amount of any and all inhibitors of glycolipid synthesis in combination with any and all agents capable of increasing the rate of glycolipid degradation. It is clear from the discussion of delivery options contemplated for the invention that the claims encompass gene therapy as a mode of treatment (see especially beginning at paragraph 56 and continued through paragraph 93).

State and level of predictability in the art: First, with regard to gene therapy, at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

With regard to agents capable of increasing the rate of glycolipid degradation administered by methods that to do not involve gene therapy, the art teaches treatment of type I Gaucher disease by administration of glucocerebrosidase or bone marrow transplantation (see

especially Platt and Butters (1998; IDS AO) the sentence bridging columns 1 and 2 on page 424 and citations therein, and the first full paragraph on page 425). However, Platt and Butters further teach that, "the major biological issue when considering enzyme replacement for the GSL storage disease is that the vast majority of these disorders, in contrast with type I Gaucher disease, have neurological phenotypes that result from GSL storage in cells of the CNS. Large glycoprotein enzymes do not cross the blood-brain barrier, and so this approach is only useful in diseases with systemic, non-CNS, storage...Also, this approach is disease specific, with each disease-specific enzyme requiring development for clinical evaluation" (page 425, paragraph 1). These teachings point out that, at the time of filing, the effective use of enzyme replacement, either alone or in combination with another agent, to treat a glycolipid storage-related disorder other than type I Gaucher disease was highly unpredictable. This is evidence by the lack of enzyme replacement therapy for a glycolipid storage-related disorder outside of type I Gaucher disease, the art recognized obstacle to development of enzyme replacement therapy for most glycolipid storage-related disorders created by the blood-brain barrier, and the recognition that success obtained with enzyme replacement therapy in the treatment of one glycolipid storage-related disorder cannot be generalized to other glycolipid storage-related disorders.

With regard to a method of treatment comprising administering an inhibitor of glycolipid synthesis wherein the primary target of said inhibitor of glycolipid synthesis is other than glucosylceramide synthase, the prior art does not provide teachings that would allow one of ordinary skill to practice the claimed invention using inhibitors of any and all enzymes involved in glycolipid synthesis. In fact, Aerts *et al.* (1998; IDS AH) teach that, "[a] disadvantage of the 'substrate deprivation' approach is that *a priori* not only the synthesis of glucosylceramide but

also that of more complex glycosphingolipids is inhibited" (page 9, paragraph 1). This teaching indicates that inhibiting the synthesis of more complex glycosphingolipids is undesirable. In view of such a teaching the skilled artisan would not predict that targeting enzymes involved in more complex glycosphingolipid synthesis would be effective in the claimed method.

Amount of direction provided by the inventor and existence of working examples: The disclosure provides examples of combined administration of the inhibitor of glycolipid synthesis NB-DNJ with two agents capable of increasing the rate of glycolipid degradation (i.e. Ceredase™ and transplanted bone marrow). The examples provided do not, however, remedy most of the deficiencies recognized in the art cited herein above. In the example of combined therapy comprising Ceredase™, applicants demonstrate only that the activity of Ceredase™ is not compromised by co-administration of NB-DNJ in normal mice and that co-administration of NB-DNJ appears to extend the half-life of Ceredase™. No evidence is provided to indicate that the combined therapy would be an effective treatment for any and all conditions of glycolipid storage-related disease, although one can speculate that the therapy could be developed for treatment of type I Gaucher disease, as Ceredase™ has been used successfully in the treatment of Gaucher disease in the past.

The findings of Example 3 (page 34) demonstrate that administration of NB-DNJ to a mouse model of Sandhoff disease following bone marrow transplantation significantly, and unexpectedly extended the survival of the Sandhoff mice beyond the survival of Sandhoff mice that received bone marrow transplantation alone. While these findings indicate that the combination of bone marrow transplantation followed by administration of NB-DNJ can be used to delay mortality as a consequence of the defect associated with Sandhoff disease, they do not

provide sufficient guidance, either alone or in combination with the teachings of the prior art, to enable one of ordinary skill to delay mortality as a consequence of any genetic defect other than the defect associated with Sandhoff disease, or to delay mortality as a consequence of the defect associated with Sandhoff disease through co-administration of NB-DNJ with any agent capable of increasing the rate of glycolipid degradation other than bone marrow transplantation.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is very high, the ordinary skilled artisan would not be able to make or use the invention commensurate with the scope of the claims without undue experimentation. The art recognizes a high degree of unpredictability in obtaining success using the methods of the instant Application. The reason for this unpredictability stems first from the lack of guidance as to how to use an agent capable of increasing the rate of glycolipid degradation outside of β-glucocerebrosidase or bone marrow transplantation, or how to use *any* agent administered by gene therapy; the lack of direction in the art with regard to how to effectively treat any glycolipid storage-related disease other than type I Gaucher disease using a method comprising an agent capable of increasing the rate of glycolipid degradation; and the art recognized barriers to generalizing success obtained in treating any given glycolipid storage-related disease to any other glycolipid storage-related disease. The teachings of the specification remedy deficiencies in the art only with respect to delaying mortality as a consequence of the defect associated with Sandhoff disease by administering NB-DNJ following bone marrow transplantation. The skilled artisan would therefore have to engage in undue experimentation to extend these findings in order to practice the method of the elected invention over any scope

beyond the treatment of type I Gaucher disease by administration of an inhibitor of glucosylceramide synthase in combination with a glucocerebrosidase enzyme.

The disclosure is not enabled for the composition claims outside of a composition comprising an inhibitor of glucosylceramide synthase with a glucocerebrosidase enzyme because, for the reasons provided above, the skilled artisan would not know how to use the compositions without engaging in undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 26 recites the limitation "inhibitor of glucosylceramide synthesis" in line 1. There is insufficient antecedent basis for this limitation in claim 1 or 25, from which claims 2 and 26 respectively depend. Claims 3, and 4 are indefinite inasmuch as they depend from claims 2.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 9-11, 14 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8 of copending Application No. 10/054,802 in view of Aerts *et al.* (*supra*). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application merely broaden the scope of the claims of the cited Application.

To the extent that they are enabled by the disclosure, the claims of the instant application are drawn to a method of treating Gaucher disease comprising administering an inhibitor of glucosylceramide synthase and a glucocerebrosidase enzyme. The claims of 10/054,802 are directed to a method of treatment comprising administering to a patient a combination of both a N-alkyl derivative of deoxynojirimycin having from about two to about twenty carbon atoms in the alkyl chain and a glucocerebrosidase enzyme. Claim 8 limits the method to treatment of Gaucher disease. It would have been obvious to one of ordinary skill in the art at the time the invention was made to broaden the scope of claims 1 and 8 from Application No. 10/054,802 to include other inhibitors of glucosylceramide synthase such that they encompass the enabled embodiments of claims 1-4, 9-11, 14 and 15 of the instant Application because Aerts *et al.* teach that compounds such as PDMP and PPMP are also effective inhibitors of the enzyme (see especially the second full paragraph on page 8).

Claims 25, 26, 33-35 and 38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 10 of copending Application No. 09/859,928 in view of Aerts *et al.* (*supra*). Again, although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application merely broaden the scope of the claims of the cited Application.

To the extent that they are enabled by the disclosure, the claims of the instant application are drawn to a composition for treating Gaucher disease comprising administering an inhibitor of glucosylceramide synthase and a glucocerebrosidase enzyme. The claims of 09/859,928 are directed to a method of treatment comprising administering to a patient a combination of both a N-alkyl derivative of deoxynojirimycin having from about two to about twenty carbon atoms in the alkyl chain and a glucocerebrosidase enzyme. In view of the teachings of Aerts *et al.* described herein above, it would have been obvious to one of ordinary skill in the art at the time the invention was made to broaden the scope of claim 10 from Application No. 09/859,928 to include other inhibitors of glucosylceramide synthase such that they encompass the enabled embodiments of claims 1-4, 9-11, 14 and 15 of the instant Application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note: The following rejection applies to the extent that the prior art discloses the same compositions and/or method embraced by the instant invention. The prior art rejection is not to be construed as an indication that the claimed or anticipated methods are *enabled* for the wide breadth of subject matter potentially embraced by the claimed method of treatment. The compositions and/or methods disclosed in the prior art are essentially enabled to the same extent as the instant specification, since there is no significant difference in the level of guidance presented in either case.

Claims 1-4, 9-11, 14 and 15 are rejected under 35 U.S.C.§102(b) as being anticipated by any one of Platt *et al.* (1998; IDS AF), Platt and Butters (1998; IDS AO) or Aerts *et al.* (1998; IDS AH).

Claim 1, and claims 2-4, 9-11, 14 and 15 as they depend from claim 1, are directed to a method for treating a glycolipid storage-related disorder, comprising administering a therapeutically effective amount of an inhibitor of glycolipid synthesis in combination with an agent capable of increasing the rate of glycolipid degradation.

Each of the cited references teach a method of treating glycolipid storage-related disorders comprising administering a an inhibitor of glycolipid synthesis (see especially Platt and Butters beginning the second paragraph on page 425 and continued through the second paragraph on page 428; Platt *et al.* beginning the fourth paragraph in column 1 and continued through the first paragraph in column 3; and Aerts *et al.* beginning the second full paragraph on page 8 and continuing through the first full paragraph on page 9). Each of the references then contemplates that the method of treating with an inhibitor of glycolipid synthesis can further comprise an agent capable of increasing the rate of glycolipid degradation (see especially Platt

and Butters, the second full paragraph on page 425; Platt *et al.*, the final sentence of the first paragraph in column 3; and Aerts *et al.* page 39, claim 15).

Claim 2 is directed to the method of claim 1, wherein the inhibitor of [glycolipid synthesis] is an imido sugar; claim 3 is directed to the method of claim 2, wherein the imido sugar is selected from the group consisting of N-butyldeoxynojirimycin (NB-DNJ), N-butyldeoxygalactonojirimycin (NB- DGN), and N-nonyldeoxynojirimycin (NN-DNJ); claim 4 is directed to the method of claim 3, wherein the imido sugar is N- butyldeoxygalactonojirimycin (NB-DGN); and claim 9 is dawn to the method of claim 1, wherein the inhibitor of glycolipid synthesis is an inhibitor of neuronal glycolipid synthesis.

Platt and Butters teach a method wherein the inhibitor of glycolipid synthesis can be NB-DNJ or N-butyldeoxygalactonojirimycin (see especially Figure 3, the caption thereto on page 426 and the list of abbreviations that appears as a footnote on page 421). Platt *et al.* teaches a method wherein the inhibitor of glycolipid synthesis is NB-DNJ and N-butyldeoxygalactonojirimycin (see especially "RESULTS" beginning in column 8, also see the definition of DGJ in the second paragraph of column 1). Aerts *et al.* teaches a method wherein the inhibitor of glycolipid synthesis is butyl-deoxynogirimycin or butyl-deoxygalactonojirimycin (see especially the second full paragraph on page 8).

Claim 10 is drawn to the method of claim 1, wherein the agent capable of increasing the rate of glycolipid degradation is an enzyme involved in glycolipid degradation and claim 11 is directed to the method of claim 10, wherein the enzyme is selected from the group consisting of glucocerebrosidase, lysosomal hexoseaminidase, galactosidase, sialidase, and glucosylceramide glucosidase.

Each of the cited references teach the enzyme glucocerebrosidase (see especially Platt and Butters, *Enzyme Replacement Therapy* on page 425; Platt *et al.*, the final sentence of the first paragraph in column 3; and Aerts *et al.*, second full paragraph on page 5).

Claim 14 is directed to the method of claim l, wherein the glycolipid storage-related disorder is selected from the group consisting of Gaucher disease, Sandhoff's disease, Fabry's disease, Tay-Sach's disease, Niemann-Pick disease, GM1 gangliosidosis, Alzheimer's disease, stroke, and epilepsy and claim 15 is directed to the method of claim 1, wherein the inhibitor of glycolipid synthesis and the agent capable of increasing the rate of glycolipid degradation are given simultaneously, sequentially, or separately.

Platt and Butters contemplates using the method to treat Gaucher disease, Sandhoff's disease, Fabry's disease, Tay-Sach's disease, Niemann-Pick disease, GM1 gangliosidosis (see especially Table I). Platt *et al.* contemplates using the method to treat Gaucher disease (see especially the final sentence in the first paragraph of column 3) as does Aerts *et al.* (see especially claim 15 on page 39). Finally, as each of the cited references teach that the method should comprise co-administration of the inhibitor of glycolipid synthesis and the agent capable of increasing the rate of glycolipid degradation, one of ordinary skill would know that the method must comprise administering the agents simultaneously, sequentially or separately.

The method taught by each of Platt and Butters, Platt *et al.* and Aerts *et al.* is the same as the method taught in the instant application, therefore the limitations of the claims are anticipated by the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25, 26, 33-35 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Platt *et al.* (1998; IDS AF), Platt and Butters (1998; IDS AO) or Aerts *et al.* (1998; IDS AH).

To the extent that they are enabled by the disclosure, the claims are drawn to a composition for treating Gaucher disease comprising an inhibitor of glucosylceramide synthase and a glucocerebrosidase enzyme in a pharmaceutically acceptable carrier, wherein the inhibitor of glucosylceramide synthesis is an imido sugar selected from the group consisting of NB-DNJ, NB-DGN, and NN-DNJ. As described herein above, Platt *et al.*, Platt and Butters and Aerts *et al.* teach all of the components of the claimed composition and a method wherein the components are administered together. The cited art does not explicitly teach that the components should be

combined in single composition or that they should be combined in a pharmaceutically acceptable carrier. There are, however, many examples in the broader art of co-administration of active ingredients in a single composition, such as co-administration of antigen and adjuvant or administration of cocktails of cancer chemotherapeutic agents, with the motivation being to administer the agent in a single convenient dose. Further, it is known in the art that any composition to be used in a method of treatment, such as the methods taught by Platt *et al.*, Platt and Butters and Aerts *et al.*, should be comprised in a pharmaceutically acceptable carrier. It would therefore have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Platt *et al.*, Platt and Butters and Aerts *et al.* such that the components are combined in a single composition for co-administration to a patient.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
October 31, 2002

JAMES KETTER
PRIMARY EXAMINER